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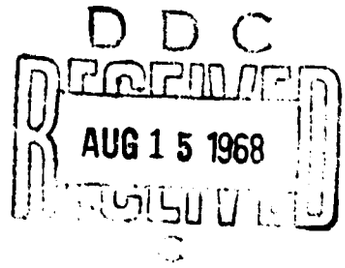

NEW VIEWPOINTS IN THE EPIDEMIOLOGY, PROPHYLAXIS AND THERAPY OF THE PLAGUE

/Following is a translation of an article by H.E. Krampitz from the Bernhard Nocht Institute for Naval and Tropical Diseases, Hamburg (Director: Dr. Dr. E.G. Nauck), in the German-language periodical Deutsch. Med. Wschr. (German Medical Weekly), Vol. 87, No. 37, 14 September 1962, pages 1853-1860./

We recognize with great astonishment that the endemic plague, which is known to the present generation of physicians of our continent only from hearsay from the obscure past, means an immediate and current medical task in the whole Western area of the USA, a country which belongs to the most civilized ones of the earth, and occasionally brings a happy camping trip by car through the mountains of California to a sudden and cruel end.

It was often attempted before, usually not very convincingly, to find answers to the simple question, why are we protected from such a misery in our age in Europe, since this epidemic raged to an unimaginable extent for at least three centuries here, and only in the XIVth century it wiped out one fourth of the total population of our continent. In the light of the newest results in the fields of the epidemiology and immunobiology of the plague, we will have to find a new answer to this question also. It is essential to find an answer to this problem, since the possibility and extent of future renewed threats to Central Europe may depend on this answer. In the last two decades, there is a considerable unrest noticeable in plague research and prevention, derived mainly from observations and experiences in Northwest and Central Africa, in the Near East, in the South of the Soviet Union, in India, Java, Madagascar, North and South America.

"Epidemiology"

A reconsideration of practically all aspects of the

plague in the whole world was already begun in Marocco in 1941, due to the initiative of Blanc, to facilitate the reconciliation of a series of opposing views in connection with the epidemiology of the disease. This meant primarly the systematic screening of animal carriers, vehicles and sources of the causative agent in long-established natural locations.

With the passing of time, the number of observations increased, that persistent endemic plague also exists, or especially exists, at those places, where commensal secondary-cosmopolitan rats are either completely absent as co-dwellers of men, or where they rarely occur, due to unfavorable environment or pest control. Although, these natural foci of the plague are long known to exist in the deserts, attributable mainly to the many infectious diseases among the Asiatic fur hunters, people were inclined for decades to consider the domestic rat population (Rattus rattus) as long-term hosts of Pasteurella pestis, especially in regard to the numerous bacteriological findings and also historical and current evidence on the transmission of the epidemic by means of transportation, namely by sea-going vessels. It can be credited to this concept that the negligent attitude toward this vermin disappeared in housing, port and ship hygiene, that the plague was repressed and no transmission occurs by marine transportation in normal times. However, the plague still remains with us as a threatening sword of Damocles, and there is no possibility to eradicate it alone with the proven conventional methods of rodent control in areas of human habitation, since it will be carried and preserved by other species of rodents, independent of civilization.

It can be safely assumed, that human bubonic plague depends as a rule on epizootics among highly susceptible rodent species, which, often enough, did not escape attention /sic/ since ancient times. To these belong, in addition to the well-known domestic rat, a large number of other, non-commensal species, such as the multiform family of the burrowing mice (Gerbillus, Meriones, Tatera, Rhombomys), squirrel species (Sciuridae), marmots (Marmota), hamsters (Cricetinae,, voles (Microtinae), and many others. There is no doubt that the plague has a tendency to disappear very quickly again in rodent populations highly susceptible to such peculiar epizootics, while the mass mortality strongly disintegrates the local habitation density of the animals, and only very few immune animals survive, if any. All attempts failed to find Pasteurella pestis in the surviving susceptible rodent species during the interepizootic period. Observations on old Kurdish natural foci brought conclusive evidence that these highly resistant rodent species, among which no mass infection or mass mortality occurs due to plague infection, have a special role in the extensive preservation of the causative agent. An animal species, which is exterminated by the plague

and is reduced to a few bacteria-free survivors, can not perform a real long-term function as a host. Such function will be more likely performed by species spared by the disease and living close to the condemned ones. The long and well known greater resistance of some small rodent species toward the plague was considered to be a limiting factor for the dissemination of the infection, until the opposite was proven to be true by systematic bacteriological examination of these species and their ectoparasites. Resistant rodents are capable of covertly sheltering the causative agent in their organs for long periods of time and of carrying infectious fleas.

Thus, it is not sufficient to look only for lymphatic node symptoms or hemorrhagic lesions, typical for the pathological courses in men and animals, in these rodents, to establish the presence of plague. The plague focus in Kurdistan, a terror to the ancient Medes 7 centuries before Christ already, is carried only by the Meriones genus of burrowing mice. According to the investigations of Misonne on mammals (1959b), there is a whole series of various species there, which at first sight are so similar to each other that a layman can hardly differentiate them. However, only 2 of these species (Meriones vinogradovi and Meriones tristrami) were shown experimentally to be highly susceptible to plague infection, while the others were just as highly resistant. These different species with opposite manners of reaction live together in the same area.

Therefore, the same game can be repeated: The epizootics selectively attack the susceptible species and drastically decimate them from time to time, while the resistant species take care that the dissemination of the causative agent is not interrupted among the rodents. The infection focus remains preserved, the animals provide the germ non-reactive residence in their bodies and take over the fleas of the dead relatives. Mammalogical analysis and bacteriological susceptibility tests showed in all cases of non-extinguished plague centers that permanent foci of biozoonotic complexes of rodent masses are responsible for these centers, complexes, which are always composed of vulnerable and resistant species. This means especially a possibly high and extensive areal density of the resistant species as "base carriers", their persistency and the possibility of using the same underground quarters undisturbed for generations, where a microclimate favorable to flea multiplication exists. When such resistant species are absent from a certain location, or they do not occur in the necessary density or not widely disseminated in space, the rodent plague becomes a temporary sensation among highly susceptible species with consequent human infections in such areas.

In the case of many historical epizootics and epidemics, transported to harbors by sea traffic, where the epidemic became extinguished very rapidly without any significant human influence, the causative agent obviously did not have a suitable local base carrier among the rodents capable of harboring a new focus. Furthermore, there are also cases known from history, where such foci glimmered for decades and the formation of a permanent focus can be assumed, until the pestilence of men and animals suddenly disappeared, giving the appearance of a redeeming miracle. In the majority of these cases, the commensal rat, especially Rattus rattus, can be regarded as the sole carrier of the causative agent and the primary source for human infection. Studies of the Iranian Pasteur Institute (Baltazard), indicated that suddenly appearing and disappearing plague outbreaks, as in Mesopotamia and Java, are recurring in certain time intervals throughout half of a century, simulating permanent foci, while these are actually only temporary structures. Cartographic studies of plague outbreaks in these areas showed that the epidemic was continuously in motion and seldom lasted longer than a year at one place. In those cases when it lasted longer, some resistant rodent species were always involved.

The explanation for this migration and the spreading of plague epizootics, with their cases of human infections, was furnished by a series of recent observations in the permanent foci of the disease. The active or passive migration of plague-infected rodents and the dissemination of their ectoparasites on the highways were occasionally overestimated. The majority of small mammals, the domestic and migratory rats being no exceptions, are loyal to their localities. When they extend the area of their occurrence, this happens gradually and step-wise over short distances by the migration of individual animals, yielding to population pressure. The passive rodent and flea transport by human land traffic does not have the assumed significance for the migration of the plague either, according to current belief. In India and Java, the plague never leaped over great distances, but proceeded step-wise from field to field, from one rodent colony to another, along "thinly wound epizootic paths" (Baltazard), until finally somewhere, at a usually unpredictable place, it meet commensal rats of human settlements, and the rats then carried the bacteria to the settlements. When there are no house or migratory rats, the carrier function can be taken over by some other facultative synoicous or commensal rodents of the great family of their species, since these animals fluctuate between the houses or huts and the surrounding open areas. Thin habitation, individual or disseminated housing favor this process. For Africa, among others, the species of Mastomys ugandae, Rattus natalensis, Arvicanthis abyssinicus, even the palm squirrel and the hibernating mouse, which visit and inhabit the grass roofs of the huts, can be

mentioned.

One must also remember, that the life profile of the house rat (and to some extent that of the house mouse) does not exist in warm countries, as we know it in Northern and Central Europe and in North America. The main masses of this animal came to us only during historical times, advancing from the warmer South and Southeast, and its occurrence is strongly connected to inhabited areas, since men is not only a provider of food to this animal, but must also protect it from cold and humidity by his walls. A so-called "open area occurrence", as can be observed in the case of the migratory rat regularly and in the case of the house mouse occasionally, can never be seen in connection with the house rat. In our climate, it would not even be possible for him. In warm countries, however, the attachment to men is broken by microclimatic conditions, and the commensal-synoicous bound between men and the house rat, very tightly knit in our areas, is suddenly loosened so completely that the animal is hardly worthy of its name. "Residence" in earth holes in the proximate or distant vicinity of settlements leads necessarly to more frequent meetings with field rodents, while on the other hand, these paramural house rats stay in continuous contact with their intramural relatives. Thus, there are wide beaten transmission paths for plague infections from steppe and field regions in the immediate vicinity of human habitation in tropical and subtropical countries, while such situation could never exist in our areas in connection with the house rat.

After these short reminescences it is understandable that it is rather difficult in individual cases to categorize the numerous rodents, which play a role in plague -- according to Pollitzer (1960) this list already contains almost 200 species -- , in addition to commensal and field species also into an intermediate category of semi-synoicous species, only on the bases of their ecological behavior toward men and his establishments. Some species should fall into separate categories at various points of the area of their distribution, while some others can be put simultaneously in all three categories at the same location. Considering the versatility and complicated organization of human habitation, it would be a hopeless task to categorize all wild animals, profiting from the agricultural activities of men, unequivocally and with universal validity into clearly separated groups , even, when one would restrict oneself to practical considerations. To a certain extent, this can be also applied to those "field inhabitants", which never voluntarly visit areas of human habitation in order to establish themselves permanently.

In view of the permanent reservoir problem of the plague, one would be inclined to divide rodents into those favored by civilization and those avoiding civilization.

Undoubtedly, it is the second group of field rodents, which is primarly responsible for the plague foci of the world, although this group can be found mainly at those places, where the surface of the earth was not yet exposed to the profoundly altering influences of human activities. Natural plague centers can not be found in areas with rationalized and intensive agriculture and cattle breeding, namely in the culture steppe, but in the wide natural steppe, semi-arid waste deserts, areas of extensive nomadic pastures and primitive agriculture, in thinly settled plateaus and bush forests in Asia, America and Central Africa.

"Causes of seasonal fluctuations in the frequency of the plague"

It is long known that the plague constantly occurs with increased frequency at certain seasons in endemic areas. It was believed for a long time that this phenomenon can be explained by simply referring to the known decisive influence of temperature and relative air humidity on the activity of fleas, especially the intensity of their multiplication, and the infection, carrier and transmitter potentials. Soon, however, contradictions became apparent in this area also, due to different situations in territories of similar climatic locations. In India and Java it can already be proven that the seasonal problem is decisively determined by a field rodent factor. At the end of the spring, during the dry-hot so-called "dead period", only the expansion of the plague comes to a stillstand; occurence of new cases of human and animal infections ceases. Surviving scattered foci in settlements show a conspicuous tendency to quickly disappear with the beginning of the summer heat, the number of affected communities decreases and new ones are not attacked. Behavioral studies on base-carrier field rodents quickly solved the puzzle, why do natural foci not spread any longer. The small mammals of open fields have a peculiar habit in protecting themselves from adverse weather in all areas with a dry-hot summer climate. They barricade themselves individually in deep, tightly sealed, underground holes, and live on provisions collected during better times. Thus, the contact of the animals, important for flea exchange, with members of their own species and facultative rodent synoicouses of human settlements, comes to an end. It is amazing to consider the small liquid requirements, which enable the field and steppe rodents, adapted to dry areas, to survive for months. Obviously, they fall into a lethargic state, initiating an inhibition of metabolic-physiological processes, similar to the hibernation of some mammals at moderate latitudes. Russian authors investigated the effect of cyclic seasonal fluctuations in the metabolic processes of the steppe shrew on its susceptibility to plague infections, and found the susceptibility the greatest during the active period, a decreasing susceptibility with the approaching winter rest period, and finally complete resistance at the beginning of hibernation. Changes in oxygen consumption and thermo-

regulation have significant roles in this process (Zhigilev and Otdelskaya, 1946; Michailov, 1956; Kalabukhov, 1958). One could probably expect mutatis mutandis similar fluctuations in the susceptibility of plague-carrying rodents in dry-hot areas during the "summer hibernation" also. Anyway, there is very little definite knowledge on their role in the "carry-over" process. In any case, permanent residence in nests in underground holes, where the mammal is also a cofactor in the determination of the microclimate, is not unfavorable to flea multiplication and to taking up of Pasteurella pestis by these fleas, even during a period characterized by humidity-saturation deficit of environmental air and unfavorable to fleas. Therefore, it is not surprising that the secondary plague appears immediately in commensal rodents and exposed human population again, when the field rodents abandon their nests and become active after the summer rest period, which is around the middle of October in India. Consequently, it is understandable that at this time new human settlements will be preferred, namely such places, which were saved of epidemic outbreaks during previous seasons.

"Formes of the pathological course of the plague"

The usual form of human bubonic plague in endemic areas is that of local and temporarly agglomerated cases, occurring individually or in small groups, with preponderantly benign courses. Only "some bubonic types have septicemic manifestations" (Seal 1960). How can and could occur then the malignant, explosively epidemic form, the "quick black death", compaired to fire striking at hay by the Arabic physician, Ibn Khatib (1348), at many places? Baltazard said in 1952, that this so-called "historical plague" practically disappeared from the modern world. The fact that such epidemic forms could not be observed in many endemic areas, especially in India, can not be explained by the simple pathogenetic assumption, according to which a portion of initially purely bubonic plague cases develop into a septicemia after overcoming the lymphatic defense wall and finally into plague pneumonia, along the organotropically traced paths, and thus, the already men-borne plague can be simply and quickly transmitted to a large group of people via droplet-infection. Since 1895, primary pulmonary plague amounted to less than 3% of all plague cases, actually to not more than 1% as a rule (Seal, 1960). The monsoon countries are certainly not lacking in periods of high air humidity. Should one probably assume the existence of Pasteurella strains with insufficient pneumotropism, or the existence of a human population possessing a resistance to the generalization of bacteria as the result of exposure for thousands of years? There is no proof for the correctness of such and similar speculations at the present.

"Transmitters and modes of transmission"

The increasing amount of knowledge on transmitters

made possible a progress through the compilation of lists of the names of infected flea species to real epidemiological qualitative concepts on the individual flea species participating in plague processes. Even within the same species, different biotypes and strains can coexist, although they differ from each other in their capacities and the duration of bacterial multiplication in the intestines, namely in their infection and vector potentials (Kartman and coworkers, 1958). More or less pronounced preferences for hosts also exist from the part of the fleas; the possible and impossible instances, the likely and consequently frequent occurrences, and rare cases, which must be rather exceptions obeying the laws of chance (transmitter potential). Great differences exist in individual endemic foci and zones of the world threatened by epidemics not only in respect to the composition of obligatory or facultative plague-carrying small mammal populations, usually consisting of completely different species, their modes of behavior characteristic of the species, and the flea indeces, but also in respect to the local habits and parasite infestation of the exposed human population of these areas.

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Plague transmission has many wheel mechanisms /sic/, and already Sticker knew (1909) that the rat → flea → men formula of plague genesis is "neither now, nor otherwise, the only one". The view point, that it is freely recognizable, is a new one.

The old concept of the bubonic plague infection of men, well supportable by animal experiments and empirically consolidated, places the sting of a rat flea at the beginning and in the foreground of the infection. First, the flea suckes on an infected rat and then permits the mass multiplication of the causative agent in its gastro-intestinal tract. Then, men is inocculated with the causative agent, after the animal deserted its rat host, killed by the plague, in a hungry state and adopts men as a "host of perplexity". Rodent fleas of various species are also the ones, who take care of the inter-individual distribution in the mammalian reservoirs.

The number of flea species, found to be spontaneously infected with Pasteurella pestis, reached, according to Pollitzer (1960), the considerable number of 100 already. Only a few species belonging to the family of Pulicidae have direct significance for men. In tropical and subtropical countries, the genus Xenopsylla with the species Xenopsylla cheopis, X. astia and X. brasiliensis are of primary importance. These species prefer commensal rats and adopt men especially gladly as a "host of substitution", while they can be found very seldom, and only individually, on rodents of open fields. There are, however, local exceptions, as everywhere, here also. The transmission of the bacteria in natural foci, and from these to commensal house rodents, is carried out by other flea species as a rule as they place themselves between rats and men. This assumption of the genesis, undoubtedly valid for tropical territories, leaves the genesis of epidemic historical plague in moderate latitudes completely in dark. Xenopsylla species can not thrive here, due to climatic conditions, since protection from the weather, successfully furnished by the domestication climate of the house rat at our latitudes, is not sufficient for these fleas. However, all altitudes and all latitudes are accessible to the plague (Stricker). The northern rat flea (Nosopsyllus fasciatus), in spite of its ominous genus name, is a typical small rodent flea, which can be found in this area not only on rats, but also on all kinds of terrestrial forest rodents, far removed from human and rat settlements; a fact for which we have a lot of proof. In case of need for a host, this flea adopts men only reluctantly, in contrast to Xenopsylla, and attempts stinging it only in exceptional cases. The fact that it transmits the plague experimentally with ease among rodents, is insignificant in regard to the possibilities of human infection transmitted by this flea. To describe it as the "European plague flea" is an expression of the past,

a fallacy committed by epidemiology, attempting to identify the historical black pestilence at our latitude with the tropical form of plague. Blanc and his coworkers must be credited with placing the role of human ectoparasites, especially the role of the human flea Pulex irritans in epidemic plague dissemination, in the proper perspective. He succeeded with the passing of time, against the initially tightly closed walls of rejection, in making probable the theory, that explosive malignant plague epidemics could not occur without the involvement of the human flea. The main argument against the degradation of rodents to the role of the dummy in the epidemic plague process, was concentrated on the central problem of the intensity and duration of blood affection by Pasteurella pestis in the course of the disease in men, which alone can guarantie the human flea an infection index sufficient for the maintenance and dissemination of such a "plague carried by men"(Sticker, 1910, Rodenwaldt, 1953). Next, most of the epidemiologists refused, to some extent passionately, to recognize the formula men $\rightleftharpoons$ human flea as possible or even probable, referring to exact theoretical calculations on how many plague bacteria are necessary to render a flea capable of infection. This happened in spite of the fact that Xenopsylla and Pulex are closely related, belonging to the same family, and that the plague was long known to vacillate between "Zoonosis" and "Anthroponosis" /sic/ in its epidemiological character.

(1943)

Blanc and Baltazard/successfully strenghtened the old textbook view, according to which the quantities of the causative agent in human blood, if they luckily appear at all, never suffice for the infection of a blood-drawing animal, or for initiating a sufficient multiplication in their intestinal tract. Thus, the intermediary role of a rodent can not be disregarded. Formerly, when the relatives and friends of a person, who died of the plague, came together to his funeral from close-by and far-away places to pay him their last respects at his internment, and each of them carried the plague home to his community, the thought was too handy to attribute the infection to inanimate objects, or to miasmatic fluid. In Marocco, the clothing, especially the undergarments, of patients died of the plague was systematically collected in tightly closed tin containers possibly immediately after their death, and searched for fleas, using necessary precautions. The results were unequivocal: The human flea (Pulex irritans) is always infected in the agonal phase on plague patients, and is capable of transmitting the acquired infection successfully by stinging susceptible laboratory rodents. The height of the blood level, namely the detectable concentration of the causative agent in peripheral blood, does not have the formerly assumed decisive significance for the infection of fleas, since they can successfully load themselves with Pasteurella by repeatedly stinging their host, whose blood (0.24 to 1.0 cubic centimeters) remains steril on artificial culture medium upon a single bacteriological examination.

It was proven in the case of human fleas also, that their sucking acts have actually a xenodiagnostic value. Blockade of the gastric passage-way in the region of the proventriculus by a bacterial clot, as the sign of violent mass multiplication of Pasteurella in that region, prevents further normal sucking action and leads to the infection of the host by the regurgitation of bacteria-containing blood into the sting wound. This phenomenon is especially marked in the case of Xenopsylla cheopis. The intestinal obstruction is not at all an essential condition for the plague infection of men and animals, according to Blanc, since the flea excrets the bacteria together with the feces through the preserved intestinal paths and lives longer in the absence of a blockade. All fleas leave a drop of feces regularly at the sting wound upon sucking blood, and this drop can be easily rubbed into the wound by clothing or can enter the body through scratching. Parasitological investigations found a high density of Pulex irritans in humane settlements in all those areas, where the plague still occurs in its epidemic form, namely in North Africa, in individual parts of the Soviet Union, in the focus connected by an over 1000 kilometer long path across of Estern Turkey, Syria, Iraq, and in individual spots in South America. In those areas however, where disseminated cases of bubonic plague do not expand into cohesive mass epidemics, and an "epidemic wave" is the result of the addition of isolated cases from a wide area, as in China, Java, Madagascar, India, and North America, such conditions of flea distribution could not be verified. Thus, the epidemic plague is a disease carried by humans, with inter-human transmission by Pulex irritans having a preference for men, it is endemic and also rodent-dependent, transmitted to men by stray members of the Xenopsylla family.

This formula seems to solve some contradictions and some pressing absurdities freely in the plague history of Western Europe. The centuries old activity of this disease left deep marks on the morals, art and literature, contributed to the shaping of history, and then disappeared completely in the 18th century without leaving behind practically any natural foci, although not without a trace. This is even more remarkable, since real natural foci show a considerable degree of obstinacy even at those places, where they most likely developed only in historical times. However, it could be stated by no means that our settlements and fields would have become free of rodents at the present time, or that the small mammals, present everywhere, would be free of fleas. On the list of plague hosts, there is a great number of eurasiatic species of small mammals, which occur often enough as inhabitants of fields, forests and meadows in our areas. Furthermore, a whole series of their closest relatives, partly from the same genera, such as burrowing mice, hamsters, squirrels, marmots and rabbit species, are also inhabitants of this latitude. The same thing is true for the flea genera of Ctenophthalmus, Megabothris, Malaraeus, Stenoponia,

Peromyscopsylla and Monopsyllus, not to mention Nosopsyllus.

"Why did the plague disappear from Europe?"

Of the three speculative-hypothetical theories for the explanation of the disappearance of the plague from Europe, one theory places the circumstances of the rat population, the second the bacteriological situation, and finally the third the flea fauna in the center of considerations.

Against the flea theory the objection could be raised, that the migratory rat did not invade Europe only in the 18th century, and not suddenly as an invasion army, neither did the migratory rat stamp out the house rat, which even at the present occurs together with it peacefully at many places. The more recent retreat of the house rat before Bandicotia bengalensis /the Bengal bandicoot/ in Indian settlements seems to verify the old experience , that the house rat as a "fugitive animal", is easily inclined to abandon previously exclusively held positions to its aggressive feeding competitor favored by the environment. The epidemiological significance of this process can not be denied, especially since the new-comers influence qualitatively and quantitatively the flea situation, as reported from India. If one would once make the effort to investigate the local rat situation in depth by personal test catches, one would soon recognize the fact, that even today there are many areas in Germany, where the house rat still rules exclusively, or areas where house and migratory rats can be alternately captured with the same effort at the same place. It is significant, that the migratory rat is more favored by civilization than the house rat, and the infection index by Nosopsyllus fasciatus is always higher for house rats living in old dry wooden houses, mills, granaries, barns, stables, etc., than in the case of migratory rats, where it always approaches the zero point more closely as more often the population in question comes in contact with water. As commensal co-dwellers of men, both species are closely connected and far removed at the same time. Thus, the belief that the house rats maintain a tighter contact with men than the migratory rats, is factually incorrect. The house rat is clearly more susceptible and endangered by Pasteurella pestis infection, while on the other hand, the resistant migratory rat seems to be qualified to act as a "base carrier".

The next hypothesis for the disappearance of the plague from Western Europe is concerned with the causative agent. Devignat (1951) regarded Pasteurella pseudotuberculosis rodentium as a mutation of the Pasteurella pestis of the Middle Ages, which displaced the great plague epizootics from Europe by means of cross-immunity; namely, both species of Pasteurella have a water-soluble common R-antigen (Thal, 1956). The thought itself is attractive, and the attempt to

ccnsider epidemiological connections in the light of a large-scale automatic protective action arranged by Nature, deserves attention (Nauck, 1958). Unfortunately, one knows practically nothing on the actual distribution and wide-range action of Pasteurella pseudotuberculosis among the domestic rodents. It also remains unclear, while did this mechanism of plague-destroying cross-immunity restrict itself only to Europe.

Of the three ideas on the disappearance of the plague in Western Europe, that one has the greatest convincing power at the present, which keeps especially in mind the human flea and the conditions of its incidence in the course of human civilization. Based upon the observations and experiences of Blanc and coworkers, and considering the possibilities, which can be derived from the distribution of rats and rat fleas in relation to men and his historical plague epidemics, Rodenwaldt made plausible the existence of the infection chain carried by humans and the human flea, basing his conclusions on the individual case of the Venetian plague in the years of 1575 to 1577. Finally, he thought that the results of his studies on local plague history could be generalized in such a fashion, "that not only that this epidemic was carried by men, the epidemic traveling from man to man mediated by Pulex irritans, but, according to reports on the plague epidemics of Western Europe in the Middle Ages and at the beginning of the Modern Age, the mode of the infection chain could not be different either in most, if not all, of the cases." The often praised well-known value of quarantine and confinement regulations in historical plague outbreaks could not be explained, if the plague of the Middle Ages could have sneaked around the country behind the backs of men along the aforementioned thin epizootic paths. The puzzle of the missing or extinguished natural foci in Europe, could be solved, considering, on one hand, the strong hold of the historical secondary plague -- smuggled into Europe -- on men and his immediate environment, and, on the other hand, the sensitivity of the naturally thin epizootic path toward the disturbance, disintegration and break up into small areas of its base-carrier rodent population by intensive agricultural land utilization, especially in a region, where the climate is not ideal. It is epidemiologically insignificant for the plague, upon the interruption of its tradition of dissemination and prevention of new epidemics from being smuggled in, whether the local suitable rodent complexes are still present, or they are developing anew.

"Preventive measures"

What are then the practical lessons to be drawn from our complete knowledge on the possible ways of existence of the plague in regard to the destruction and prevention of the disease? The campaign against the blood-sucking rodent

and house vermin, which directly transmits the infection, should stand in the front line of preventive endeavors, both long-term and immediate emergency measures. Upon the disinfection of houses, huts, warehouses and stables, performed according to the large scale method of mosquito eradication with contact insecticides, a greater attention should be paid to floors, all damp corners, rodent passages, holes and nests in beams and roofs made of straw, reed, or grass, but especially the living areas, underneath beds, bed mats and closets, when aiming at fleas and their brood, than in the case of mosquito eradication. Usually, it is possible to control the endangering expansion of the epidemic quickly by using only these emergency measures, giving special consideration to the houses of infected persons and their neighborhoods. The low point reached presently by the disease, as at no other time in history, can be primarly attributed to contact insecticides. When the necessity of immediate and promptly effective prophylaxis arises in the case of an epidemic outbreak, the Expert Committee of the World Health Organization justly regards the introduction of quarantines, wide-range campaigns against rodents and prophylactic mass inocculations as wasting of time, money and effort. The last two measures, however, will be always working components of a long-term prophylaxis. For general planning of housing hygiene, the modern contact rodenticides became indispensible. For the prevention of the import and dissemination of commensal plague-carrying rodents as "blind passengers" on land, see and air vehicles, Paragraphs 49 to 55 of the International Sanitary Regulations of the World Health Organization make clear recommendations to the official health services of the individual states. According to this, the entry of any person to any country should not depend on a prophylactic plague inocculation. The incubation period for the plague is established as 6 days, similarly the quarantine period for suspected persons, counted from the time of the last exposure, namely presence at places, where rodent plague is active.

In reference to the possibilities of a successful therapy of the environmental organism, namely the elimination of obstinate, partly ancient, natural foci, great pessimism dominated the scene for decades, considering the enormous extent of these infected areas. The problem of the possible eradication of the plague in the world means primarly the elimination of these permanent foci. Plague specialists in the Soviet Union proved by their efforts of over 30 years, that resignation is not in order even in such difficult situations. In the steppes of the Caspian low lands, a great plague focus, carried by ground squirrels (Citellus pygmaeus), exists for centuries. Only between 1913 and 1934, 700 endemic individual foci became known in the steppes around the Northern coast of the Caspian see. Until 1932, activities were restricted to campaigns against steppe rodents in smaller areas, where enzootic or endemic plague was reported. Success, how-

ever, failed, since cleaned-up small areas were resettled again from their peripheries, and the causative agent very quickly found new carrier populations at such places. Lasting success was only achieved, when in 1933 a systematic large area eradication was introduced, which embraced 7 million hectars yearly, 45 million hectars up to the present time, parts of these areas requiring several treatments. The easily located, relatively large ground squirrel holes were systematically searched for by a labor force comprising ten-thousands of people, and individually treated with a hydrocyanic acid preparation or with chloropicrin ($CClNO_2$). In the 116 million holes not only the ground squirrels, but also their nest parasites, were exterminated at the same time, therefore, they could not migrate and could not increase the danger of plague for the human population of this area. The results verified the theory that actually only the base-carrier, in this case Citellus pygmaeus, is alone responsible for the preservation of the plague, if it occurs at a certain density across of wide areas. The eradication campaign can be restricted to the possibly strong rarefication of this settlement density. Then, even without a complete eradication of the carrier, epizootics are no more possible. The presence of one or two individuals per hectar is unobjectionable; before the eradication campaign, there used to be 20 to 80 per hectar in the Caspian steppes. Not a single case of plague is known to have occurred in the armies around Stalingrad, operating at the boundaries of a former large enzootic plague territory. Between 1942 and 1955, the pestilence existed only in a small border region and became completely extinct in the main centers; it has to be seen, whether for good or not. Soviet authors are nevertheless cautious (Kusnetzow, 1932 to 1934, Fenyuk, 1960).

"Therapy"

As long as such actions will not reach the roots of the misery, prophylactic and therapeutic medical activities for the benefits of plague-threatened or plague-infected humans will remain essential parts of the campaign against this infection. Considering the value of protective inoculation and the possibility of acquiring an active immunity, one should remember the observation made already by Sticker, that one can recover three times from the plague and become its victim at the fourth time. Occasional failures of prophylactic inoculation will therefore not be surprising. Immune reactions in men, especially after a single inoculation, are very different individually, regardless of the vaccine used, and the antibody formation is often completely insufficient. Therefore, reconvalescents are not necessarly predestined to work in nursing, laboratories, and in field assignments safely for life time. In the case that this must happen for a short period of time, medical prophylaxis is the method of choice for the reduction of the danger of exposure. This can be accomplished by the administration of modern sulfonamides,

especially those with prolonged stability in the blood, such as the oral administration of 3.0 grams of sulfa-combinations (supronal, protocid, triple sulfonamides) daily for 6 consecutive days, or, according to the recommendations of the World Health Organization, intramuscular administration of 1.0 gram streptomycin , or 1.0 to 2.0 grams of a tetracycline preparation for 5 days. Sulfonamides are to be used therapeutically also. A dosage of 1.5 /second figure can not be clearly read in the text/ to 2.0 grams every 4 hours is recommended for 14 days, or until the temperature decreases, whereby the therapy should begin with an initial thrust of 4.0 grams sulfonamide intravenously when necessary, for patients in delirium the parenteral follow-up should be maintained, and in desolate cases a continuous drop-infusion added to maintain a level of 10-20 miligrams per 100 milliliters of blood.

Penicillin failed so clearly in plague therapy, that even in combination therapy with sulfonamides (aritocillin, syncillin, sulfa-tardocillin, etc.), it has no real advantages in comparison with pure sulfonamides. These drugs alone decreased the mortality of septicemic plague from 90% to about 23%, and the mortality of bubonic plague to exactely 6%.

Streptomycin and the broad-spectrum antibiotics on tetracycline and chloramphenicol basis proved to be valuable in contrast to penicillin. The streptomycin dosages, successfully used by individual authors, decreased considerably, however. In 1952, the World Health Organization recommended 16-20 grams by intramuscular administration for 6-7 days in the case of pulmonary plague. Girard (1952) was compelled to give 25 grams for 6 days to his adult patients, while in the case of a child 11.5 grams were sufficient. He recommended to divide the total dosage into 0.5 gram individual doses every 3 hours during the first two days of the treatment, and to increase the intervals of administration to 4 hours beginning on the third day. For aureomycin 2.5 - 7.5 grams daily, in individual doses of 250 miligrams every 2 hours, are suggested. In the case of chloramphenicol, a total therapeutic dosage of 20-25 grams intravenously, or 0.5 gram orally at every 3 hours, proved to be satisfactory.

For a practical therapeutic procedure, the World Health Organization recommends the following basic rules: Plague cases should be detected as fast as possible and effective therapy begun immediately. As a rule, bubonic plague can be controlled by sulfonamides alone in all of its phases. When they are not successful, or incompatibility is indicated, antibiotic therapy must be applied. All cases of primary or secondary pulmonary plague should be immediately treated with antibiotics. One should always remember to reduce the antibiotic dosage whenever possible, and to replace it with corresponding doses of sulfonamides, and to attempt to treat

cases initially well responding to antibiotic therapy with sulfonamides as soon as it is possible. In all cases of the disease, hospitalization should be energetically attempted for epidemiological and clinical reasons, and strict bed-rest must be prescribed. Easily digestible food and, especially in the case of sulfonamide therapy, sufficient liquid intake should be assured. According to Girard (1946), renal complications can be best meet by sufficient alkali substitution. An urine pH of 7.2 is considered to be optimal. The application of modern sulfonamide preparations will also reduce the danger of concrement formation.

Any manipulations of the buboes in the acute inflammatory phase are strongly counter-indicated (incision, drug injection). For analgesic local therapy, ointment bandages (20% ichthyol) with supplementary belladonna are effective. /due to illegible words in the text, the translation of this sentence is only an approximate one/ The opening of lymphatic node abscesses is only permitted in the case of a total fluctuation. The cleaning process is not facilitated by repeated examina tions and care of the incision wound. The healing process will best proceed, when there is as little as possible disturbance, and the bandage is changed only seldom (Pollitzer, 1954).

Before efficient drugs were available for plague therapy, efforts to develop an effective prophylactic vaccination were the only possible means of plague prevention, in addition to campaigns for the eradication of /the adjective used is illegible; it probably reads: four-legged/ house and ship vermins. These possibilities still exist at the present for long-term prophylaxis. After the use of reconvalescent sera gave discouraging results, for understandable reasons, Haffkine (1896/97) was the first to develop a prophylactic vaccination procedure. He obtained his vaccine from rabbits immunized by a bouillon culture of Pasteurella pestis, killed at 70°C after one hour. Since that time the Haffkine vaccine was mainly applied in India, in 40 million doses, with partly good results. Girard in Madagascar (1926) and Otten in Java (1936) each developed a vaccine, independently of each other, from live plague bacteria strains with a diminished virulence (Tiwiday and E.V. /?/ strains). This vaccine proved to be superior to the Haffkine vaccine in outbreaks in the 1930s. Similar live vaccines from local strains proved to be equally efficient in the Soviet Union. Russian authors pointed out that intracutaneous vaccination can lead to local allergic reactions, whose intensity can serve as a measure of the developing immunity. The great disadvantages of the live vaccine were its limited stability, especially in tropical climate, and the difficulties involved in the preparation of large quantities. Nevertheless, it was possible in

Madagascar to vaccinate 800,000 of one million inhabitants with live vaccine (0.5 milliliters twice) and to reduce plague lethality by 2/3. Since then, live vaccine is the choice of preference in prophylactic plague vaccination. Only the special demands, as encountered by the American Army health services during the armed conflict in Korea, lead again to turning away from the hard-to-handle live vaccine (Meyer and Forster, 1948)."None of the known vaccination methods is completely satisfactory", said Meyer, "since only 60% of the vaccinated persons will develop effective immunity in the best case".

Meyer prepared from washes of virulent Pasteurella pestis cultures (grown on solid culture media, detoxified, killed by formalin, and supplied with an excess of aluminum hydroxide) a vaccine, which seems to satisfy all requirements. Good lasting immunity will be achieved only after three repeated vaccinations, where the last one should follow after a period of 3-6 months. This last vaccination is primarly responsible for suddenly raising the immune-body level. Antibody determination by hemagglutination test and complement fixation, using purified antigens, can serve as basis for an accurate evaluation of the vaccine and the immunity state of vaccinated persons. Only in the case of good antibody formation will the septicemic course and the plague pneumonia not develop. In the combination of the propylactic plague vaccination with the typhoid-paratyphoid vaccine, a synergistic action became apparent in regard to plague immunity. Chemotherapy shows quicker and better results with vaccinated persons, than with non-vaccinated ones. Undesirable local or general side effects will not occur at the first vaccination with formalin-killed bacteria. Since the protective action of the vaccination can not be expected before 10-20 days, decisively only after half a year (third vaccination), the active immunization has a great value as a long-term preventive measure, but has very little or no value shortly before or during an epidemic (Meyer, 1960).

"The confirmed plague refutes all cures", writes resignedly the Arabian physician Chalin de Vinario in 1382. It remains unclear, what was the reputation of some physicians in the Middle Ages based on, physicians, who achieved a special reputation in the eyes of their contemporaries for their successes in the treatment of the plague. The influence of personality, with or without applications to the plague, alone, secret incenses and the remedies of the "healing filth pharmacy" could have hardly impressed the Black Death. However, the fact that the plague always had a tendency to spontaneously disappear locally, with or without effective human aid, might have contributed to the undeserved fame of some of them. Today, the swords are sharpened against the plague, not all of them being very keen, the majority is still pretty unwieldy, but they made it possible that the yearly legions of millions of plague victims were reduced to 300 cases in the whole world. This situation is not a secular wave trough any

more, as observed in the mass gradation /sic/ of many epidemics, without men being able to assume some direct role in fighting the pestilence, but it is obviously the fruit of knowledge and action; only they will prevent in the future also the threatening rise of new secular wave crests everywhere in the world.

"Summary"

A complete review of the essential newer aspects of the epidemiology, prevention, and therapy of the plague is submitted in the form of a summary report. The presented opinions essentially correspond to those expressed by the members of the expert committee of the World Health Organization in recent years. In the epidemiology of the disease, the great significance of resistant rodent species in the local long-term preservation of the causative agent in natural foci, is emphasized. Possibilities and ways of transmission, and the seasonal variations in the incidence of plague, are influenced by the peculiar mode of life of the base-carriers among rodents to a much greater extent as hitherto believed. The conditions for the occurrence of a malignant explosively epidemic course of the disease are discussed, pointing out the role of the human flea (Pulex irritans) in the plague process. Of the three main theories for the explanation of the disappearance of the plague from Europe in the Modern Age, the greatest convincing force is attributed to that one, which places the human flea and its conditions of incidence in the process of civilized history in the center of arguments. In the case of preventive actions, difference will be made between immediate emergency measures and long-term prophylaxis. The first consist of disinfection and medical protection of exposed persons, the latter of preventive vaccination and rodent eradication. In preventive vaccination, vaccines from killed bacteria are again strongly propagated today. Practical procedures are individually outlined for plague therapy by sulfonamides and antibiotics, underlining the complete uselessness of penicillin.

"Bibliography"

Comprehensive and almost complete collections can be found by Sticker (1910) and Pollitzer (1954, 1960). Sources mentioned in the text, but not referred to again, should be seen in the text.

/In the absence of instructions, only the 3 references shown below were thought to require translation/:

A. Grumbach and W. Kikuth: The infectious diseases of men and their causative agents (Stuttgart, 1958)
E. Rodenwaldt: The plague in Venice in 1575-1577. A contribution to the problem of infection chains in plague epidemics in Western Europe (Heidelberg, 1953)

G. Sticker: Treatise from the history of the plague and the science of the plague, in the first volume of "The Plague" (Giessen, 1908-1910).

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